REMARKS/ARGUMENTS

Claims 24-35 and 38-60 are pending in the present application. Claims 29, 30, 33-35, 41, 42, 46, 48, 52, 53 and 55-58 have been withdrawn from consideration. Claims 1-23, 36 and 37 have been canceled without prejudice or disclaimer. Claims 24 and 25 have been amended by this Amendment.

Claim Rejections under 35 USC § 102 and 35 USC § 103

Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 stand rejected under 35 USC § 103(a) as anticipated by Adeyinka et al. (Clin. Cancer Res., vol. 78, pp. 3788-3795, 2002, hereinafter "Adeyinka") in view of Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999, hereinafter "Sgroi"). Claims 59 and 60 stand rejected under 35 USC § 103(a) as unpatentable over Adeyinka and Erlander et al. (US 2003/0186248, hereinafter "Erlander"). Applicants respectfully traverse these rejections.

Discussion of Disclosed Embodiments

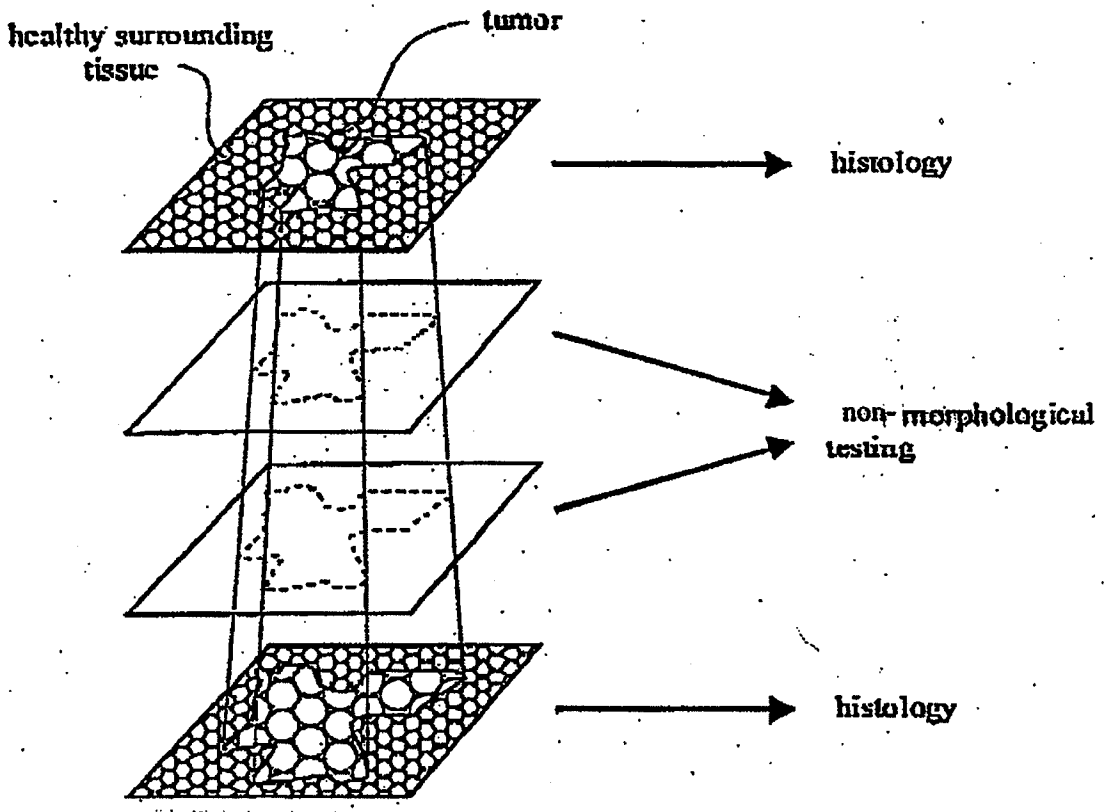
The following descriptive details are based on the specification. They are provided only for the convenience of the Examiner as part of the discussion presented herein, and are not intended to argue limitations which are unclaimed.

Applicants' disclosed embodiments are directed to reducing an error which is caused by healthy tissue in a sample to be analyzed. At least two sections of a microtome section series of a tissue sample that are not immediately adjacent to each other are stained and evaluated histologically/cytologically, while other sections of the microtome section series that are located between these two sections in the original tissue sample are homogenized and subjected to non-

morphological analytical testing such as, for example, to an array-based mRNA analysis. These sections are selected so that the section or sections sent for non-morphological analytical testing were located between the two sections for histological/cytological evaluation, in situ (in the tissue sample). (See, e.g., paragraph [0054] of the application as originally filed).

The tissue-specific composition of the two flanking sections is thus known, and the molecular-biological characteristics of the one or more sections located between the flanking sections in the original tissues sample are also known. The quantitative fraction, the appearance, and/or the distribution pattern of the diseased tissue or diseased cells in the sections or sections analyzed by the molecular-biological methods can thus be more reliably determined. (See, e.g., paragraphs [0055]-[0057] of the application as originally filed).

Similar advantages apply to disclosed embodiments in which the divided samples, i.e., samples or portions of samples, that are sent for histological/cytological examination are selected to ensure that the one or more divided samples sent for non-morphological analytical testing were located between these divided samples in situ. (see paragraph [0058] of the application as originally filed). The Example Figure shown below illustrates one or more divided samples sent for non-morphological analytical testing that were located between these divided samples in situ.



EXAMPLE FIGURE

In other words, Applicants disclosed embodiments are directed to an arrangement of at least four tissues section as shown in the Example Figure, in which the at least two sections which undergo the non-morphological testing, (e.g., the molecular biology), are sandwiched between two sections which undergo histological testing.

Arguments

The art cited by the Examiner fails to disclose, teach or suggest "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared

sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by Applicants' independent claim 24.

The Examiner, in the Response to Arguments section of the current Office Action, asserts that this is precisely what Sgroi teaches. In particular, the Examiner asserts that Sgroi teaches selecting sections for LCM from within the sections used for morphological testing, since Sgroi teaches using the adjacent sections, i.e., on either side of the LCM sections, and, therefore, the LCM sections are internal to the sections used for morphological testing. The Examiner then asserts that Sgroi teaches analyzing several consecutive sections to the LCM sections morphologically in Fig. 3B. Applicants disagree because (1) Fig. 3B of Sgroi shows stained slides of three different types of cells and (2) Sgroi discloses only pairs of tissue sections.

Sgroi, including the portion thereof cited by the Examiner in the Office Action, teaches only pairs of tissues sections, and fails to disclose teach or suggest an arrangement of at least four tissue sections, as shown in the above Example Figure, in which at least two sections that undergo non-morphological testing, (e.g., the molecular biology), are sandwiched between two sections which undergo histological testing.

Sgroi describes analysis of tissue sections from a breast cancer using histology and microarray hybridization. Immunohistochemical staining of frozen tissue sections adjacent to slides used for laser capture microdissection (LCM) is performed (See p. 5657, col. 2, first paragraph of Sgroi).

Sgroi discloses in the last paragraph on 5659 that "we performed immunohistochemical analysis of apolipoprotein using tissue sections that were adjacent to those used for laser miscrodissection". Sgroi explains on page 5660 in the description of Fig. 3B that "consecutive

tissue sections corresponding to those used for LCM (cDNA arrays and RTQ-PCR) were immunoperoxidase stained". These portions of Sgroi both refer to pairs of tissue sections. In other words, two sections in total are disclosed as analyzed in the Sgroi's experiment. Sgroi fails to disclose, teach or suggest an arrangement of at least four tissue sections, as shown in the above Example Figure, in which at least two sections undergo the non-morphological testing, (e.g., the molecular biology), are sandwiched between two sections which undergo histological testing. There is no teaching in Sgroi that the LCM sections are internal to the sections used for morphological testing, and the Examiner's position that "adjacent sections" teach sections within or internal to the morphological sections is simply incorrect. "Adjacent sections" do not require sections that are internal to other sections.

That is, Sgroi fails to teach or suggest that the immunohistochemical staining is performed on a slide of a tissue sample that was arranged in situ between two tissue samples used for the LCM. To the contrary, Sgroi teaches only immunohistochemical staining of frozen tissue sections adjacent to slides used for laser capture microdissection (LCM). Immunohistochemical staining of a merely adjacent slide does not allow for a more reliable determination because a tissue fraction range cannot be determined from slides that are merely adjacent. The two of prepared sections instead must be selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is between the two of the prepared sections in situ, i.e., in the original sample tissue. Sgroi therefore fails to disclose, teach or suggest "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical

testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by Applicants' independent claim 24.

Moreover, Adeyinka, Sgroi and Erlander, whether considered alone or in combination, fail to disclose, teach or suggest the quantitative limitations of the claimed invention, which allows Applicants to calibrate the results of the non-morphological testing arithmetically by means of the results obtained in the cytological/histological examination. As noted above, the quantitative fraction, the appearance, and/or the distribution pattern of the diseased tissue or diseased cells in the sections or sections analyzed by the molecular-biological methods can thus be more reliably determined. (see, e.g., paragraphs [0055]-[0057] of the application as originally filed). This quantitative analysis can only be performed if the sections which undergo the non-morphological testing are sandwiched between two sections which undergo histological testing, so that the gradients of tumor/stroma distribution in the sample can be accounted for in the analysis. Adeyinka, Sgroi and Erlander are completely unrelated to such quantitative aspects of the claimed invention because Adeyinka, Sgroi and Erlander fail to teach or suggest "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by Applicants' independent claim 24.

Therefore, even assuming, *arguendo*, the propriety of the Examiner's proffered combination of Adeyinka, Sgroi and Erlander (which Applicants do not concede), Erlander fails to cure the deficiencies of Adeyinka and Sgroi discussed above with respect to independent claim 24. Erlander simply describes the use of molecular histological signatures to interpret and correlate

cytological specimens, and fails to disclose, teach or suggest at least another one of the prepared sections subjected to the non-morphological analytical testing is between the two of the prepared sections in situ.

Independent claim 24 is accordingly deemed to be patentably distinct over the cited art for at least the foregoing reasons.

Independent claim 25 contains features akin to those discussed above with respect to claim 24 and, therefore, claim 25 is likewise deemed to be patentably distinct over the cited art for at least the same reasons as is claim 24. Claims 26-35 and 38-60, which variously depend from one of claims 24 and 25, are deemed to be patentably distinct over the cited art for at least the same reasons as are claims 24 and 25, as well as on their own merits.

In view of the foregoing, Applicants respectfully request that the rejections under 35 USC § 102 and 35 USC § 103 be withdrawn.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections, and allowance of all pending claims is respectfully solicited.

It is believed that no fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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